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RE: "PROGNOSIS AFTER BREAST CANCER DIAGNOSIS IN WOMEN EXPOSED TO ESTROGEN AND ESTROGEN-PROGESTOGEN REPLACEMENT THERAPY"

Bergkvist et al. (1) observed a significantly higher survival rate in breast cancer patients who had received estrogen treatment than in those who had not. The authors stated that, to their knowledge, this had not been previously studied. I wish to point out that this report confirmed several earlier studies, with none to the contrary, indicating a better prognosis for breast cancer in estrogen users than in nonusers (2–4). In 1976, Burch et al. (2) were the first to observe a 25 percent reduction in mortality from breast cancer when the malignancy developed in hysterectomized estrogen users. In my study of 256 postmenopausal women with breast cancer, the mortality rate was 22.2 percent in the 63 hormone users compared with a rate of 45.5 percent in the 165 nonusers, a difference which was statistically significant at $p \leq 0.05$ (3). In an English study of 4,544 hormone users, the mortality from breast cancer was significantly reduced, with a relative risk of 0.55 (95 percent confidence interval 0.28–0.96) (4).

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In accordance with Journal *policy, Dr. Bergkvist and his colleagues were asked if they wished to respond to Dr. Gambrell's letter but chose not to do so.*

RE: "CASE-CONTROL STUDIES USING OTHER DISEASES AS CONTROLS: PROBLEMS OF EXCLUDING EXPOSURE-RELATED DISEASES"

Pearce and Checkoway (1) express concern that in a case-control study, exclusion of controls admitted to a hospital (or registry) for diseases that are related to the exposure under study may introduce, rather than eliminate, bias in a registry-based study. In particular, they suggest that if controls are selected from a set of diseases, some of which are positively associated and some of which are negatively associated with the exposure under study, the positive and negative biases may cancel each other out, making exclusion of controls with exposure-related diseases unnecessary. We are concerned that this advice may lead to biased

estimates of risk, since one can never be sure that the effects of multiple biases will, in fact, be canceled out. We prefer strict application of the exclusion principle for registry-based studies, which would result in the exclusion of all controls diagnosed with any disease associated with exposure, either positively or negatively.

In Pearce and Checkoway's discussion of example 2 and table 2 (1), a preference for not excluding disease 1, which is positively related to exposure, from the control group in a registry- (hospital-) based case-control study is indicated. It is argued that the aggregate of all the diseased controls should be used because their exposure distribution is the same as that in the study base. In the contrived example, it happens that not excluding any of the disease groups gives the same estimate of relative risk as the true risk ratio of 2.00. However, even an ideal control group would not yield an estimate of exactly 2.00, because the odds ratio calculated from the study base (the "traditional" way (1)) is (20/40)/(920/3,720) = 2.02, not 2.00, a consequence of the study disease's not being rare. The joint effects of 1) a strong positive association between disease 1 and exposure, 2) the weaker negative associations between exposure and diseases 2–5, and 3) the effect of the violation of the rare disease assumption cancel out perfectly in the example; therefore, sampling from the entire group of diseased controls gives the (expected) estimate of 2.00. A slight change, however, in any of the exposure-disease relations, in the proportion of subjects without any disease, or in the relative prevalences of the different diseases would eliminate the exact correspondence between the risk ratio based on the entire population and the odds ratio based on a control group of all subjects without the study disease in the registry. It seems presumptuous to assume that several biases will cancel each other out, particularly when some of the biases are unknown and will remain unknown even upon completion of the study.

In the malignant lymphoma study (2) cited in their Discussion (1), Pearce and Checkoway based their decision to use other cancer patients as controls on national mortality data which indicated that New Zealand farmers had the same cancer rates as the rest of the country. Thus, their strategy for control selection was based on a quantitative assumption (an odds ratio of exactly 1 when the base is defined to include all cancer cases) drawn solely from external vital statistics data. We would rather rely on qualitative a priori assumptions (associations of exposure with specific forms of cancer).

An overall lack of association between farming and total cancer mortality may not indicate that a particular exposure related to farming is not associated with overall cancer mortality. The difference in the odds ratio estimates of 1.3 and 0.9 for ever being potentially exposed to chlorophenols using other cancer controls and general population controls, respectively (2, table 7), is somewhat disturbing, and suggests potential bias in the cancer control group. Alternatively, this difference may have been due to chance, information bias, or some other bias operating in the series of population controls. A comparison of the empirical effects of several different exclusions would provide further insight into the appropriateness of using cancer controls, as opposed to general-population controls, in this study. Specifically, what is the impact of making no exclusions, i.e., using all other cancer cases as controls; excluding subjects with the exposure-related cancers identified by Blair et al. (3); or using subjects diagnosed with cancer at any of a small number of sites that have never been shown to be related to exposure and for which there is no prior reason for suspecting a relation?

Miettinen comments, "The need is to have *defensible inclusions*, and there is *no need to defend exclusions*" (4, p. 82). Our strategy regarding exclusion of controls with exposure-related diseases from registry-based studies can be summarized as "When in doubt, throw them out!" The payoff for a potentially small extra effort in the study design will be more convincing results. If a liberal exclusion policy makes selection from the registry infeasible, a population-based study might be considered, especially when, as in the example, the catchment area for cases is the general population.

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THE AUTHORS REPLY

We thank Drs. Wacholder and Silverman (1) for their observations. Our paper (2) was written to show that the belief that exposure-related diseases should automatically be excluded from a control group of "other diseases" is not valid as a general principle. In their letter, Wacholder and Silverman argue for "strict application of the exclusion principle" (1, p. 1018).

Wacholder and Silverman certainly may be correct if their intention is to assert that the exclusion principle will usually yield valid results. However, we do not agree that it will always yield valid results, and we believe that selection of controls requires careful consideration of the circumstances in each particular study rather than routine application of this general

principle. This is because, as we have shown (2), a disease which may be unrelated to exposure in one population may be (indirectly) related to exposure in another. Thus, decisions on inclusion or exclusion often require information about the actual population under study. In some circumstances, at least, such information will yield more valid decisions than will a priori assumptions (based on data from other populations or no data at all).

Wacholder and Silverman cite as justification for their argument Miettinen's comment on the need to have "defensible inclusions" (3, p. 82) and to use a disease "whose occurrence is known to be unrelated to the determinant under study" (4, p. 548). This line of reasoning is theoretically correct, but in practice it is not verifiable. In fact, it is no more useful than a proposal that one select a control disease "that gives the right answer."

The problem is *how* to find a control disease or group of diseases which reflects the exposure prevalence in the study base (i.e., which is unrelated to exposure). In practice, it is usually impossible to do this by the "defensible inclusion" approach, because most exposure-disease associations have not been studied adequately, especially those which were negative initially. Usually, the only diseases for which there is no reason to suspect an association with exposure are those that have never been studied.

Thus, the only practical options are usually either using all other diseases as controls or using all other diseases but excluding those known to be related to exposure. Wacholder and Silverman have argued for the latter option. This certainly may be a valid approach most of the time. However, as we have shown, there are exceptions to this rule, and it should not be applied blindly.

Finally, Wacholder and Silverman's comment about the rare disease assumption is not relevant to our paper, since we specifically discussed the option of sampling from the entire base population, and showed that (in contrast to the more traditional method of sampling which Wacholder and Silverman use) it would give valid results without any need for a rare disease assumption.

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